METHODS FOR TREATMENT OF CANCERS

RELATED APPLICATION

The present application claims priority to U.S. Provisional Application No. 63/179,089, filed on April 23, 2021, the entire contents of which are hereby incorporated by reference for all purposes.

BACKGROUND

Neurotensin, a 13 amino acid neuropeptide, is implicated in the regulation of luteinizing hormone and prolactin release and has significant interaction with the dopaminergic system. Neurotensin is bound by neurotensin receptors, which include, among others, neurotensin receptor 1 (NTSR1).

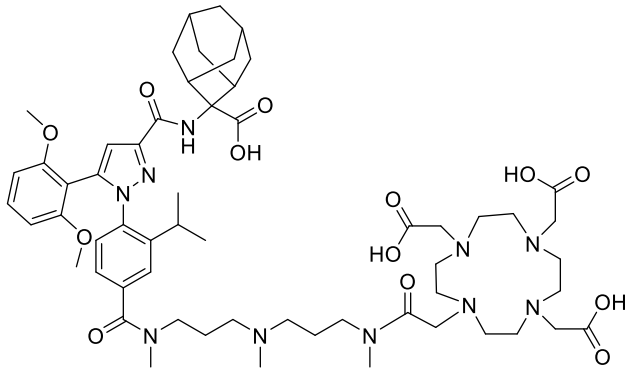
NTSR1 is expressed predominantly in the central nervous system and intestine (smooth muscle, mucosa, and nerve cells). In addition, NTSR1 is highly expressed in a mammalian body and a human body, in particular on several neoplastic cells in several tumor indications, whereas the expression of NTSR1 in most other tissues of the mammalian and the human body is either not existent or low.

Because of this selective expression, NTSR1 is regarded as a suitable target for diagnostic agents, as well as for drugs for treating cancers such as colorectal cancer and pancreatic cancer.

There is a need to develop new methods of using NTSR1 binders for treating cancers.

SUMMARY

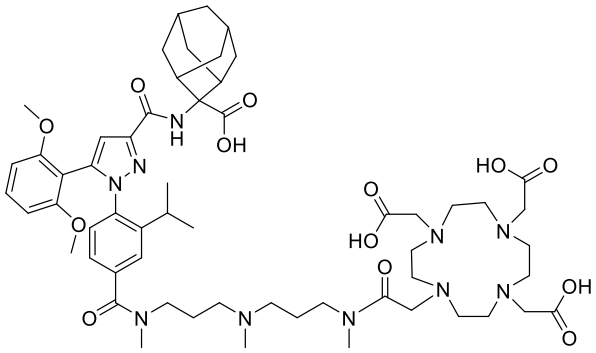
In a first aspect of the present disclosure, there is provided a use of an ^{225}Ac-radiopharmaceutical in the manufacture of a medicament for treating cancer, wherein said ^{225}Ac-radiopharmaceutical comprises ^{225}Ac chelated with a compound of Formula I:



(I),

wherein the compound binds to neurotensin receptor 1 (NTSR1) and does not cross the blood-brain barrier, and wherein said ^{225}Ac-radiopharmaceutical is to be administered to a subject at a dosage of less than 10 MBq/kg of body weight of said subject or is to be administered as a unitary dosage of less than 40 MBq to said subject.

The present disclosure relates to a method of treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of an actinium-225 (^{225}Ac)-radiopharmaceutical, said ^{225}Ac-radiopharmaceutical comprising ^{225}Ac chelated with a compound of Formula I:



(I),

wherein the compound binds to NTSR1 and does not cross the blood-brain barrier, and wherein said ^{225}Ac-radiopharmaceutical is administered at a dosage of less than 10 MBq/kg of body weight of said subject or is administered as a unitary dosage of less than 40 MBq to said subject.

In some examples, said subject is an animal (e.g., mouse) or a human (e.g., patient). In some examples, said subject is a human (e.g., patient having cancer).

In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of less than 8 MBq/kg (e.g., less than 6 MBq/kg, less than 4 MBq/kg, less than 2 MBq/kg, less than 1 MBq/kg, or less than 0.5 MBq/kg) of body weight of said subject. In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of less than 1 MBq/kg of body weight of said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of less than 250 kBq/kg (e.g., about 225 kBq/kg or less, about 200 kBq/kg or less, about 175 kBq/kg or less, about 150 kBq/kg or less, about 125 kBq/kg or less, about 100 kBq/kg or less, about 75 kBq/kg or less, about 50 kBq/kg or less) of body weight of said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of 50-250 kBq/kg (e.g., 50-225 kBq/kg, 50-200 kBq/kg, 50-175 kBq/kg, 50-150 kBq/kg, 50-125 kBq/kg, 50-100 kBq/kg, 75-250 kBq/kg, 75-225 kBq/kg, 75-200 kBq/kg, 75-175 kBq/kg, 75-150 kBq/kg, 75-125 kBq/kg, 75-100 kBq/kg, 100-250 kBq/kg, 100-225 kBq/kg, 100-200 kBq/kg, 100-175 kBq/kg, 100-150 kBq/kg, 100-125 kBq/kg) of body weight of said subject. Each of the dosage can be administered as a single dosing or in multiple times (e.g., 2 times, 3 times, 4 times, or more as needed). In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of 75-225 kBq/kg of body weight of said subject. In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of 100-200 kBq/kg of body weight of said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of about 250 kBq/kg, about 225 kBq/kg, about 200 kBq/kg, about 175 kBq/kg, about 150 kBq/kg, about 125 kBq/kg, about 100 kBq/kg, about 75 kBq/kg, or about 50 kBq/kg of body weight of said subject. Each of the dosage can be administered as a single dosing or in multiple times (e.g., 2 times, 3 times, 4 times, or more as needed). In some examples, said ^{225}Ac-radiopharmaceutical is administered at a dosage of about 150 kBq/kg of body weight of said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage of less than 30 MBq, e.g., 1-28 MBq, 3-25 MBq, 5-20 MBq, 5-15 MBq, or 10-15 MBq to said subject. As used herein, "unitary dosage" typically refers to a single dose. To perform the method of this present disclosure, said ^{225}Ac-radiopharmaceutical can be administered as a unitary dosage for multiple times (e.g., 2 times, 3 times, 4 times, or more as needed), i.e., administered multiple doses. When said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage for multiple times, each unitary dosage can be same or different.

In some examples, said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage of less than 20 MBq to said subject. In some examples, said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage of 5-15 MBq to said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage of about 6 MBq, about 8 MBq, about 10 MBq, about 12 MBq, about 14 MBq, about 16 MBq, or about 18 MBq to said subject.

In some examples, said ^{225}Ac-radiopharmaceutical is administered as a unitary dosage of about 10 MBq to said subject.

In some examples, the method of this present disclosure can be used for treating a cancer selected from the group consisting of colorectal cancer, pancreatic ductal adenocarcinoma, small cell lung cancer, prostate cancer, breast cancer, meningioma, Ewing's sarcoma, pleural mesothelioma, head and neck cancer, non-small cell lung cancer, gastrointestinal stromal tumors, uterine leiomyoma, and cutaneous T-cell lymphoma.

In some examples, said cancer is selected from one of the following NTSR1-expressing advanced, metastatic and/or recurrent solid tumors: pancreatic ductal adenocarcinoma (PDAC), squamous cell carcinoma of the Head and Neck (SCCHN), colorectal cancer (CRC), gastric cancer, neuroendocrine differentiated (NED) prostate cancer, and Ewing's sarcoma.

In some examples, said cancer is colorectal cancer, pancreatic ductal adenocarcinoma, small cell lung cancer, prostate cancer, breast cancer, meningioma, or Ewing's sarcoma.

In some examples, said cancer is colorectal cancer or pancreatic ductal adenocarcinoma.

In some examples, the method of this present disclosure further includes administration of an imaging agent that comprises a radioactive isotope chelated compound of Formula I as a

diagnosis means to determine eligibility of the subject being treated (e.g., a cancer patient) as it relates to NTSR1 expression.

In some examples, the radioactive isotope is selected from the group consisting of ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{99m}Tc, and ^{111}In. In certain examples, the radioactive isotope is ^{68}Ga, ^{89}Zr, or ^{111}In.

In various examples above, said ^{225}Ac-radiopharmaceutical is administered intravenously.

The details of one or more examples of the disclosure are set forth in the description below. Other features, objects, and advantages of the disclosure will be apparent from the below drawing, description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic depicting the group average animal weights ± standard deviations (g) for [^{177}Lu]-3BP-227 radiotherapy at 2.1 mCi and 4.5 mCi dosages.

FIG. 2 is a schematic depicting the group average animal weights ± standard deviations (g) for [^{225}Ac]-3BP-227 radiotherapy at 1 µCi and 3 µCi dosages.

FIG. 3 is a schematic depicting the group average animal tumor volumes ± standard deviations (mm^3) for [^{177}Lu]-3BP-227 radiotherapy at 2.1 mCi and 4.5 mCi dosages. Tumor volume (TV) was calculated as TV = 0.52 x (L x W^2) where L (length) is the longest diameter of the tumor and W (width) is the shortest diameter of the tumor.

FIG. 4 is a schematic depicting the group average animal tumor volumes ± standard deviations (mm^3) for [^{225}Ac]-3BP-227 radiotherapy at 1 µCi and 3 µCi dosages. Tumor volume (TV) was calculated as TV = 0.52 x (L x W^2) where L (length) is the longest diameter of the tumor and W (width) is the shortest diameter of the tumor.

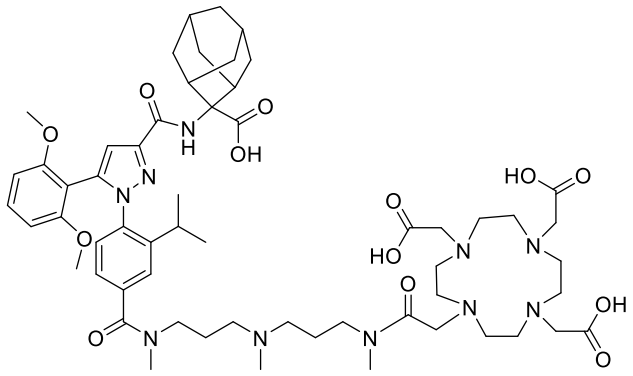
FIG. 5 is a schematic depicting the group average percentage relative weights ± standard deviations for [^{177}Lu]-3BP-227 radiotherapy at 2.1 mCi and 4.5 mCi dosages. Percent relative weight was calculated for a given animal as the percentage of its weight at day n compared to its weight at day 0.

FIG. 6 is a schematic depicting the group average percentage relative weights ± standard deviations for [^{225}Ac]-3BP-227 radiotherapy at 1 µCi and 3 µCi dosages. Percent relative weight was calculated for a given animal as the percentage of its weight at day n compared to its weight at day 0.

CLAIMS

What is claimed is:

1. Use of an ^{225}Ac-radiopharmaceutical in the manufacture of a medicament for treating cancer, wherein said ^{225}Ac-radiopharmaceutical comprises ^{225}Ac chelated with a compound of Formula I:



(I),

wherein the compound binds to neurotensin receptor 1 (NTSR1) and does not cross the blood-brain barrier, and wherein said ^{225}Ac-radiopharmaceutical is to be administered to a subject at a dosage of less than 10 MBq/kg of body weight of said subject or is to be administered as a unitary dosage of less than 40 MBq to said subject.

2. The use of claim 1, wherein said subject is a human.

3. The use of claim 2, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of less than 1 MBq/kg of body weight of said subject.

4. The use of claim 3, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of less than 250 kBq/kg of body weight of said subject.

5. The use of any one of claims 1-4, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of 75-225 kBq/kg of body weight of said subject.

6. The use of any one of claims 1-4, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of 100-200 kBq/kg of body weight of said subject.

7. The use of any one of claims 1-4, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of about 75 kBq/kg, about 100 kBq/kg, about 125 kBq/kg, about 150 kBq/kg, about 175 kBq/kg, about 200 kBq/kg, or about 225 kBq/kg of body weight of said subject.

8. The use of claim 7, wherein said ^{225}Ac-radiopharmaceutical is to be administered at a dosage of about 150 kBq/kg of body weight of said subject.

9. The use of claim 2, wherein said ^{225}Ac-radiopharmaceutical is to be administered as a unitary dosage of less than 20 MBq to said subject.

10. The use of claim 9, wherein said ^{225}Ac-radiopharmaceutical is to be administered as a unitary dosage of 5-15 MBq to said subject.

11. The use of claim 9, wherein said ^{225}Ac-radiopharmaceutical is to be administered as a unitary dosage of about 6 MBq, about 8 MBq, about 10 MBq, about 12 MBq, about 14 MBq, about 16 MBq, or about 18 MBq to said subject.

12. The use of claim 9, wherein said ^{225}Ac-radiopharmaceutical is to be administered as a unitary dosage of about 10 MBq to said subject.

13. The use of claim 1, wherein said cancer is selected from the group consisting of colorectal cancer, pancreatic ductal adenocarcinoma, small cell lung cancer, prostate cancer, breast cancer, meningioma, Ewing's sarcoma, pleural mesothelioma, head and neck cancer, non-small cell lung cancer, gastrointestinal stromal tumor, uterine leiomyoma, and cutaneous T-cell lymphoma.

14. The use of claim 13, wherein said cancer is colorectal cancer, pancreatic ductal adenocarcinoma, small cell lung cancer, prostate cancer, breast cancer, meningioma, or Ewing's sarcoma.

15. The use of claim 13, wherein said cancer is colorectal cancer or pancreatic ductal adenocarcinoma.

16. The use of claim 1, wherein an imaging agent that comprises a radioactive isotope chelated compound of Formula I is to be further administered to the subject.

17. The use of claim 16, wherein the radioactive isotope is selected from the group consisting of ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{89}Zr, ^{99m}Tc, and ^{111}In.

18. The use of claim 16, wherein the radioactive isotope is ^{68}Ga, ^{89}Zr, or ^{111}In.

19. The use of any one of claims 1-18, wherein said ^{225}Ac-radiopharmaceutical is to be administered intravenously.